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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,186	07/13/2001	Mary Jeanne Kreek	600-1-284N	3062

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KLAUBER & JACKSON
411 HACKENSACK AVENUE
HACKENSACK, NJ 07601

EXAMINER	
SAKELARIS, SALLY A	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/905,186	KREEK ET AL.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-60* is/are pending in the application.

4a) Of the above claim(s) *48-58, 60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-47 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *72002* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *2 Sequence alignments* .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 31-47 and 59 in the Paper filed 4/30/2003 is acknowledged. Applicant's arguments filed 04/30/03 have been fully considered but they are not persuasive. Applicant should note that while their election included all kit claims(59-61), only one will be examined as SEQ ID NO:2 was not elected for further prosecution, only C510T within SEQ ID NO:1 and therefore only kit claim 59 will be examined. The traversal is on the ground(s) that the office has mischaracterized the groups since the examiner failed to "define compositions and methods, with properties so distinct as to warrant separate examination and search". Applicant argues that the methods of group II "could not be achieved without the variants identified by Applicants" but they are reminded that the restriction requirement read that; "Inventions I and II are related as products and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product **or** (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the polynucleotides of invention I can be used in a materially different process such as for creating a haplotype for the human orphanin FQ/nociceptin receptor gene". Applicants also submit that the examination of Group I and II can be made without serious burden. The examiner maintains that the requirement for a single variant that falls in the coding region(ie. a single sequence) is appropriate as nucleotide sequences with different compositions are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute independent

and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide sequences are presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141 et seq. As such, applicant's request for reconsideration for inclusion of 2 additional variants that fall into the coding region of human orphanin FQ/nociceptin receptor gene, that are identified in claims 31 as A804G and C1026T is denied and the restriction requirement made on 3/20/2003 is made final as the examiner maintains each group is correctly separated as unrelated or patentably distinct entities.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. The present application's claim to benefit of a U.S. provisional Application 60/218,205 filed July 14, 2000, is granted.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 31-47 and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 31-47 and 59 are indefinite over the recitation of "a variant allele of a human orphanin FQ/nociceptin receptor gene, comprising a DNA sequence having at least one variation in SEQ ID NO:1, wherein said variation comprises C510T". The actual placement of the variation "C510T" is not defined by the claim, the specification does not provide a standard

for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. There is no fixed definition in the art for what constitutes the DNA sequence having at least one variation in SEQ ID NO:1, wherein said variation comprises C510T. It is unclear if position C510T represents the 510th nucleotide in the open reading frame, or in the entire sequence as submitted in applicant's listing or alternatively as listed in their figures 1 and 7 corresponding to SEQ ID NOS 1 and 7 respectively. It is further unclear if the wild type at this position is a "C" or a "T". Applicant must amend the claims to clarify the exact variant and its exact location in the proper SEQ ID NO that is being claimed.

B. Claims 31-47 and 59 are indefinite over the recitation of "a variant allele" as it is unclear how the sequence to which this is referring, is variant. It is unclear where the variation occurs, what the variation is, with what frequency it occurs, what effect the variation has, nor a description of to what "non-variant" sequence this "variant" sequence is being compared. Applicant should amend the claim to elucidate the characteristics of the variation being claimed. For example, Applicant could amend the claims to indicate that the variant is identical to SEQ ID NO:Y with the exception that the variant contains a "T" at position X of SEQ ID NO:X.

35 U.S.C. 101/112 Utility Rejections

35 U.S.C. 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Definitions: [from REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS; repeated from http://www.uspto.gov/web/menu/utility.pdf]

> "Credible Utility" - Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as

being "wrong". Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility. A *credible* utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use. For example, no perpetual motion machines would be considered to be currently available. However, nucleic acids could be used as probes, chromosome markers, or forensic or diagnostic markers. Therefore, the credibility of such an assertion would not be questioned, although such a use might fail the *specific* and *substantial* tests (see below).

"Specific Utility" - A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be *specific* in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)

C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial, and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

Note that "throw away" utilities do not meet the tests for a *specific* or *substantial* utility. For example, using transgenic mice as snake food is a utility that is neither specific (all mice could function as snake food) nor substantial (using a mouse costing tens of thousands of dollars to produce as snake food is not a "real world" context of use). Similarly, use of any protein as an animal food supplement or a shampoo ingredient are "throw away" utilities that would not pass muster as specific or substantial utilities under 35 U.S.C. ' 101. This analysis should, or course, be tempered by consideration of the context and nature of the invention. For example, it a transgenic mouse was generated with the specific provision of an enhanced nutrient profile, and disclosed for use as an animal food, then the test for specific and substantial *asserted* utility would be considered to be met.

"Well established utility" - a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. "Well established utility" does not encompass any "throw away" utility that one can dream up for an invention or a nonspecific utility that would apply to virtually every member of a general class of materials, such as proteins or DNA. If this is the case, any product or apparatus, including perpetual motion machines, would have a "well established utility" as landfill, an amusement device, a toy, or a paper weight; any carbon containing molecule would have a "well established utility" as a fuel since it can be burned; any protein would have well established utility as a protein supplement for animal food. This is not the intention of the statute.

See also the MPEP at 2107 - 2107.02.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 31-47 and 59 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility due to its not being supported by either specific and/or substantial utility or a well established utility.

The claimed variant allele of the human orphanin FQ/nociceptin receptor gene is not supported by a specific asserted utility because the disclosed method of producing a human

orphanin FQ/nociceptin receptor from a silent polymorphic variant is not specific and is generally applicable to any nucleic acid. The specification teaches that the variants may be used to determine altered levels of gene expression as a consequence of the presence of one or more of the polymorphisms described in the specification. An example of such a method comprises the steps of culturing a unicellular host transformed or transfected with an expression vector comprising a variant allele which is operatively associated with a promoter. The transformed or transfected unicellular host is then cultured under conditions that provide for expression of the variant allele of the human orphanin FQ/nociceptin receptor gene, and the expression product is recovered from the unicellular host. Additionally, the specification teaches a method for determining a susceptibility of a subject, and determining whether either the first or second alleles, or both alleles comprise a DNA sequence having at least one variation in SEQ ID NO:1. The specification omits any teaching though of what susceptibility can be detected through the detection of a specific allele. A method of determining susceptibility of pain in a subject is disclosed but no results including a connection to any specific alleles are presented in the specification. All of the aforementioned are non-specific uses that are applicable to nucleic acid(s) in general and not particular or specific to the nucleic acid(s) required to perform the claimed methods.

Further, the claimed methods are not supported by a substantial utility because no substantial utility has been established for the claimed subject matter. For example, a nucleic acid may be utilized to obtain a protein. The protein could then be used in conducting research to functionally characterize the protein. The need for such research clearly indicates that the protein and/or its function is not disclosed as to a currently available or substantial utility. A starting material that can only be used to produce a final product does not have substantial asserted utility in those instances where the final product is not supported by a specific and substantial utility. In this case none of the proteins that are to be produced as final products resulting from processes involving claimed nucleic acid have asserted or identified specific and substantial utilities. The research contemplated by applicants to map genomes, physical mapping, positional cloning, and in functional genomics does not constitute a specific and substantial utility. Identifying and studying the properties of a protein itself or the mechanisms in which the protein is involved does not define a "real world" context or use. Similarly, the

other listed and asserted utilities as summarized above or in the instant specification are neither substantial nor specific due to being generic in nature and applicable to a myriad of such compounds. The claimed methods require the use of a nucleic acid, a variant allele of SEQ ID NO:1, for which a specific and substantial utility has not been established. Additionally, the specification has not established a specific and substantial utility for any of the nucleic acid variant alleles. Accordingly, methods of determining susceptibility of pain in a subject through the expression of variant alleles in SEQ ID NO:1 constitutes a research project. While one could perform methods that search for alterations in SEQ ID NO:1, then assay these alterations to try to determine whether the alterations are associated with the occurrence of susceptibility to pain, such a use even if found is not specific or substantial. Note, because the claimed invention is not supported by a specific and substantial asserted utility for the reasons set forth above, credibility has not been assessed. Neither the specification as filed nor any art of record discloses or suggests any property or activity for the nucleic acid method such that another non-asserted utility would be well established for the claimed methods.

Claims 31-47 and 59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 31-35, 38-40, and 42-47 are rejected under 35 U.S.C. 102(b) as being anticipated by Mollereau et al.(FEBS Letters 341 (1994)).

Applicant should note that in light of the indefinite-ness rejection made above, the examiner is interpreting the claimed subject matter, and thus applying art as applicable to, a DNA sequence comprising the variant C510T as listed in SEQ ID NO:1. The 510th position had been determined by counting 509 nucleotides from the "A" in the start codon "ATG" at position 689 of SEQ ID NO:1 and therefore placing the variant at position 1198 in SEQ ID NO:1, the 510th nucleotide after the "ATG". The variant is further being interpreted as a "C" at this position as in SEQ ID NO:1 as the enclosed alignment of SEQ ID NO:1 and Mollereau's X77130 show variation but still share this variant allele of the ORL1 gene.

Mollereau et al. teach the cloning, functional expression and localization of human ORL1(Accession number X77130) a novel member of the opioid receptor family. The reference teaches that a "clone (named hORL1) was isolated, sequenced and found to encode a protein of 370 amino acids whose primary structure displays the seven putative membrane-spanning domains of a G protein-coupled membrane receptor" (Abstract). The isolated variant of ORL1 was further detectably labeled with a radioactive element and was used to isolate, and subsequently isolate itself, a clone to which it was able to hybridize(Pg. 34, 2.1). Next, the reference teaches a cloning vector, pTZ18R comprising the isolated variant of hORL1 and an origin of replicationPg. 34, 2.1). Mollereau further teach an isolated fragment of 1953 bp containing the entire coding region of hORL1 as being subcloned in plasmids pSVL and pRC/CMV. The reference further teaches that PSVL:hORL1 was used to transfect COS-7 cells and pRC/CMV:hOLR1 to transform CHO-K1 cells(Pg. 34, 2.3). Mollereau et al. continue that

the hORL1 receptor is most closely related to opioid receptors not only on structural(sequence) but also functional grounds: hORL is 49%-50% identical to the murine mu opioid receptors"(Abstract). Furthermore, the reference includes an alignment of the mu opioid receptor sequence and that of ORL1(Fig. 2) to show the relative identities. The reference also asserts that the three major types of opioid receptors(Mu, Delta and Kappa) act primarily via G proteins to inhibit adenylyl cyclase and/or calcium channels or to stimulate potassium channels. Mollereau et al. teaches that in light of findings through the work done on these opioid receptors(esp. delta) and because of its apparent similarities with other G protein-coupled membrane receptors, the attempt was made to clone new members of the opioid family. The reference teaches PCR amplification of highly conserved portions of the delta opioid receptor and its use to isolate hORL1. The use of similar sequences such as other opioid receptor gene sequences was successfully used to isolate this new member of the opioid receptor family which has been found to exhibit substantial sequence identities with opioid receptors and once stably transfected into CHO-K1 cells, mediates inhibition of adenylyl cyclase by etorphine, a nonselective opiate agonist.

4. Claims 31-47 are rejected under 35 U.S.C. 102(b) as being anticipated by Yu et al.(US Patent 6,103,492).

Applicant should note that in light of the indefinite-ness rejection made above, the examiner is interpreting the claimed subject matter, and thus applying art as applicable to, a DNA sequence comprising the variant C510T as listed in SEQ ID NO:1. The 510^{th} position had been determined by counting 509 nucleotides from the "A" in the start codon "ATG" at position 689 and therefore placing the variant at position 1198 in SEQ ID NO:1, the 510^{th} nucleotide after

the "ATG". The variant is further being interpreted as a "T" at this position as in SEQ ID NO:7, and the wild type allele as a "C" that is present in SEQ ID NO:1. This sequence is being determined as any variant opioid receptor comprising the "T" albeit from any organism(rat for example) and with any other variations present(See alignment).

Yu teach polynucleotides encoding the mu opioid receptor polypeptides, the recombinant vectors carrying those sequences and the recombinant host cells including either the sequences or vectors. Yu also teaches a rat cDNA SEQ ID NO: 16 that has at least one variation comprising the "C510T" or "T" variant listed in SEQ ID NO:1, at nucleotide 1198, or any combination thereof.(Please see attached alignment) Yu further teaches the isolated variant allele in SEQ ID NO:16 and an isolated nucleic acid molecule selectively hybridizable to the isolated variant allele(Col. 18, lines 18-31)being detectably labeled(Col. 18 lines 32-34) with a radioactive element(Col. 18, line 36). The reference goes on to teach cloning vectors comprising an isolated opioid receptor gene(SEQ ID NO:16) with an origin of replication(Col. 25 line 8) and cloning vectors with a sequence that is hybridizable to said opioid receptor gene(Col. 15 lines 63-67 and Col. 15 lines 1-5). The reference further teaches a cloning vector wherein SEQ ID NO:16 can be prepared from genomic DNA libraries using lambda phage technologies(Col. 15 line 62). Yu additionally teaches expression vectors comprising the isolated variant allele of C510T and an isolated nucleic acid molecule selectively hybridizable to said variant allele of C510T(Col. 26), both operatively associated with a promoter(Col. 30 line 31) of the lac system(Col. 30, lines 31 and 52), and the 3-phosphoglycerate kinase promoter(line 56). Additionally, Lu teaches a unicellular host transformed/transfected with the above expression vectors encompassing both the SEQ ID NO:16 and those sequences hybridizable to the same(Col. 18 lines 18-31 and Col. 25

lines 7-10)) each one operatively associated with a promoter(Col. 25 lines 20-25) wherein said host comprises E. coli(Col. 30 line21) and cell lines of the Chinese Hamster Ovary(Col. 31 lines 19). Lastly, Yu teaches diagnostic assay kits for detecting the presence , in a biological sample, of a polynucleotide for the mu opioid receptor of the present invention. The kit also contains reagents for detecting an interaction between an agent and a receptor of the present invention(Col. 45 and 46). The reference teaches generally that means are needed for the identification of the DNA sequences encoding individual opioid receptors. Given such isolated, recombinant sequences, it is possible to address the heretofore intractable problems associated with design and testing of isofirm-specific opiod receptor agonists and antagonists. The reference lastly asserts that the availability of cDNAs encoding the opioid receptors will permit detailed studies of signal transduction mechanisms and reveal the anatomical distribution of the mRNAs of these receptors, providing information on their expression pattern in the nervous system.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 31-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mollereau et al.(FEBS Letters 341 (1994)) in view of Yu(US Patent 6,103,492).

Applicant should note that in light of the indefinite-ness rejection made above, the examiner is interpreting the claimed subject matter, and thus applying art as applicable to, a DNA sequence comprising the variant C510T as listed in SEQ ID NO:1. The 510^{th} position had been determined by counting 509 nucleotides from the "A" in the start codon "ATG" at position 689 of SEQ ID NO:1 and therefore placing the variant at position 1198 in SEQ ID NO:1, the 510^{th} nucleotide after the "ATG". The variant is further being interpreted as a "C" at this position as in SEQ ID NO:1 as the enclosed alignment of SEQ ID NO:1 and Mollereau's X77130 show variation but still share this variant allele of the ORL1 gene.

Mollereau et al. teach the cloning, functional expression and localization of human ORL1(Accession number X77130) a novel member of the opioid receptor family. The reference teaches that a "clone (named hORL1) was isolated, sequenced and found to encode a protein of 370 amino acids whose primary structure displays the seven putative membrane-spanning domains of a G protein-coupled membrane receptor" (Abstract). The isolated variant of ORL1 was further detectably labeled with a radioactive element and was used to isolate, and subsequently isolate itself, a clone to which it was able to hybridize(Pg. 34, 2.1). Next, the reference teaches a cloning vector, pTZ18R comprising the isolated variant of hORL1 and an

origin of replicationPg. 34, 2.1). Mollereau further teach an isolated fragment of 1953 bp containing the entire coding region of hORL1 as being subcloned in plasmids pSVL and pRC/CMV. The reference further teaches that PSVL:hORL1 was used to transfect COS-7 cells and pRC/CMV:hOLR1 to transform CHO-K1 cells(Pg. 34, 2.3). Mollereau et al. continue that the hORL1 receptor is most closely related to opioid receptors not only on structural(sequence) but also functional grounds: hORL is 49%-50% identical to the murine mu opioid receptors"(Abstract). Furthermore, the reference includes an alignment of the mu opioid receptor sequence and that of ORL1(Fig. 2) to show the relative identities. The reference also asserts that the three major types of opioid receptors(Mu, Delta and Kappa) act primarily via G proteins to inhibit adenylyl cyclase and/or calcium channels or to stimulate potassium channels. Mollereau et al. teaches that in light of findings through the work done on these opioid receptors(esp. delta) and because of its apparent similarities with other G protein-coupled membrane receptors, the attempt was made to clone new members of the opioid family. The reference teaches PCR amplification of highly conserved portions of the delta opioid receptor and its use to isolate hORL1. The use of similar sequences such as other opioid receptor gene sequences was successfully used to isolate this new member of the opioid receptor family which has been found to exhibit substantial sequence identities with opioid receptors and once stably transfected into CHO-K1 cells, mediates inhibition of adenylyl cyclase by etorphine, a nonselective opiate agonist.

Mollereau et al. do not teach their isolated nucleic acid molecule that is hybridizable to the isolated variant allele of hORL1 to be detectably labeled with a radioactive element nor do they teach the cloning vector comprising a bacteriophage further comprising lambda derivatives.

However, Yu teach polynucleotides encoding the mu opioid receptor polypeptides, the recombinant vectors carrying those sequences and the recombinant host cells including either the sequences or vectors. Yu also teaches a rat cDNA SEQ ID NO: 16 that has at least one variation comprising the "C510T" or "T" variant listed in SEQ ID NO:1, at nucleotide 1198, or any combination thereof.(Please see attached alignment) Yu further teaches the isolated variant allele in SEQ ID NO:16 and an isolated nucleic acid molecule selectively hybridizable to the isolated variant allele(Col. 18, lines 18-31)being detectably labeled(Col. 18 lines 32-34) with a radioactive element(Col. 18, line 36). The reference goes on to teach cloning vectors comprising an isolated opioid receptor gene(SEQ ID NO:16) with an origin of replication(Col. 25 line 8) and cloning vectors with a sequence that is hybridizable to said opioid receptor gene(Col. 15 lines 63-67 and Col. 15 lines 1-5). The reference further teaches a cloning vector wherein SEQ ID NO:16 can be prepared from genomic DNA libraries using lambda phage technologies(Col. 15 line 62). Yu additionally teaches expression vectors comprising the isolated variant allele of C510T and an isolated nucleic acid molecule selectively hybridizable to said variant allele of C510T(Col. 26), both operatively associated with a promoter(Col. 30 line 31) of the lac system(Col. 30, lines 31 and 52), and the 3-phosphoglycerate kinase promoter(line 56). Additionally, Yu teaches a unicellular host transformed/transfected with the above expression vectors encompassing both the SEQ ID NO:16 and those sequences hybridizable to the same(Col. 18 lines 18-31 and Col. 25 lines 7-10)) each one operatively associated with a promoter(Col. 25 lines 20-25) wherein said host comprises E. coli(Col. 30 line21) and cell lines of the Chinese Hamster Ovary(Col. 31 lines 19). Lastly, Yu teaches diagnostic assay kits for detecting the presence, in a biological sample, of a polynucleotide for the mu opioid receptor of

the present invention. The kit also contains reagents for detecting an interaction between an agent and a receptor of the present invention(Col. 45 and 46). The reference teaches generally that means are needed for the identification of the DNA sequences encoding individual opioid receptors. Given such isolated, recombinant sequences, it is possible to address the heretofore intractable problems associated with design and testing of isoform-specific opioid receptor agonists and antagonists. The reference lastly asserts that the availability of cDNAs encoding the opioid receptors will permit detailed studies of signal transduction mechanisms and reveal the anatomical distribution of the mRNAs of these receptors, providing information on their expression pattern in the nervous system.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to practice the teachings of Mollereau et al. in view of Yu on the basis of high homology of hORL1 to well known opioid receptors such as the mu opioid receptor and thus the applicability of similar techniques. The practioner of ordinary skill in the art would have used the similarities shared by the family of opioid receptor genes as taught by Mollereau and others in the art, as the motivation to alter the compositions specific to the mu opioid receptor in view of the ORL1 gene for the expected benefit of the hORL1 gene having similar characteristics and results that would provide more information regarding hORL1 because of the well known identity that exists between the two receptor types in the art.

6. Claims 31-47 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mollereau et al.(FEBS Letters 341 (1994)) and in view of Yu (US Patent 6,103,492) and in further view of Ahern(The Scientist, Vol. 9, 1995).

The teachings of Mollereau in view of Yu are summarized above but omit the teaching of including directions for use in the kit of claim 59.

However, Ahern teaches that buying premade reagents and kits are convenient and they save time. The reference also teaches that a kit that supplies all the necessary reagents for a particular research application should also provide detailed instructions to follow.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to practice the teachings Mollereau and Yu in view of Ahern to have include directions in the kit to have provided detailed instructions to follow making the kit easier to work with.

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (703) 306-0284. The examiner can normally be reached on Monday-Thursday from 7:30AM-5:00PM and Friday from 1:00PM-5:00PM.

If attempts to reach the examiner are unsuccessful, the primary examiner in charge of the prosecution of this case, Carla Myers, can be reached at (703)308-2199. If attempts to reach the examiners are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)308-1119. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (703)605-1237.

Sally Sakelaris

6/24/2003

CARLA J. MYERS
PRIMARY EXAMINER